FORMULATION AND EVALUATION OF FLOATING MICROSPHERE OF BERBERINE HYDROCHLORIDE FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

*Namrata Singh
India.

ABSTRACT
Arthritis a chronic progressive disease characterized by synovial inflammation, autoantibody production, bone and cartilages destruction. In addition to the local lesion occurring in the joints systemic symptoms including cardiovascular, pulmonary, psychological and skeletal disorders are also common in patients with RA. Berberine is considered to be a predominantly selective Jak3 antagonist. Data from kinase assays and protein-compound docking simulation show that berberine blocked Jak3 catalytic activity after binding to the kinase domain of Jak3. Floating microspheres are gastro-retentive drug delivery system based on non-effervescent approach. The floating microsphere alters the absorption of the drug thus enhancing the bioavailability. They prolong the dosing intervals which will allow developing once a day formulation and thereby increasing patient compliance beyond the level of existing dosage form by achieving control over gastric residence time. Berberine with wide range of biological activity possesses low absorption. This was selected for the studies as it is poorly absorbed in the lower GIT and have short elimination half life. The floating microsphere beneficially alters the absorption of the drug and enhancing bioavailability. They prolong the dosing interval which will allow to develop once a day formulation and thereby enhance patient compliance beyond the level of existing dosage forms by achieving the control over gastric residence time. Floating microsphere are gastro retentive drug delivery system based on non effervescent approach. They floats over gastric content for long period of time. As the system floats over the gastric content the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.
KEYWORDS: Berberine hydrochloride, Floating Microsphere, Rheumatoid Arthritis, HPMC, Tween 80 Etc.

1.1 INTRODUCTION

Arthritis is the name given to a number of over 100 medical conditions that affect the musculoskeletal system. Arthritis often causes pain in the joints. Joint-related arthritis problems are the most common form of arthritis; however systemic arthritis can affect the whole body. The impact of arthritis on women depends on the type of arthritis that each woman has, but many arthritis conditions may be very painful and debilitating. Women are more likely to get arthritis than men, but the reasons for this are not exactly known. It’s a chronic progressive disease characterized by synovial inflammation, autoantibody production, bone and cartilages destruction. In addition to the local lesion occurring in the joints systemic symptoms including cardiovascular, pulmonary, psychological and skeletal disorders are also common in patients with RA (1). (fig;1).

Fig 1.1: Normal and Arthritic Joints.

Symptoms of Arthritis

Different symptoms may be experienced with different types of arthritis. Most types of arthritis will include the following symptoms.

• Pain and stiffness in the joints;
• Swelling around the joints;
• Difficulty in moving a joint;
Warmth or redness in a joint.

**Diagnosis of Arthritis**

It is often difficult to diagnose arthritis because many of the symptoms can by symptoms of other diseases. In making a diagnosis, your doctor may perform some of the following:

- **Physical exam Looking for**
  - Swelling redness and deformity in joint.
  - Checking how easily joints can be moved.
  - Examining heart, lungs, eyes, ears and throat.
  - Blood tests.

### 1.2 PATHOGENESIS OF DISEASE

The underlying disease mechanisms remain unclear but are generally triggered by infections and inflammatory mediators. At the articular borders, in a result of ongoing inflammation the lining layer forms a pannus that invades the adjacent articular cartilage and subchondral bone. Synovial T cells are attracted by chemokines and receive survival signals such as IL-7 and IL-15. The pannus formation is composed of infiltrating cells, such as monocytes/macrophages, as well as RA synovial fibroblasts. They secrete proinflammatory cytokines and chemokines that perpetuate inflammation. In addition, they release receptor activator of nuclear factor-kappa B ligand (RANKL) and promote osteoclast differentiation, leading to bone destruction. Cartilage undergoes damage by catabolic effects in chondrocytes after their stimulation by cytokines. Proteins from the synovial tissue of RA patients are extensively phosphorylated by intracellular tyrosine kinases, proving the importance of tyrosine kinases in the pathogenesis of RA. Post-transcriptional and post-translational events further regulate mediator production. The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway has received less attention than other signaling pathways. However, several cytokines implicated in RA pathogenesis, including IL-6, IL-1, and interferons (IFNs), activate the JAK/STAT pathway, moreover STAT3 is constitutively activated in RA (2).
Genetic susceptibility

1.3 BERBERINE HYDROCHLORIDE

Berberine, an isoquinoline alkaloid, quaternary ammonium salt from the protoberberine group of benzylisoquinolinealkaloids has been reported to ameliorate various autoimmune diseases including rheumatoid arthritis by oral administration. However, its mechanism remains mysterious due to an extremely low bioavailability. The fact that berberine readily accumulates in the gut, the largest endocrine organ in the body, attracted us to explore its antiarthritis mechanism in view of the induction of intestinal immunosuppressive neuropeptides. It is found in many medicinal plants, such as Berberis (e.g. Berberis vulgaris–barberry, Berberis aristata– tree turmeric, Mahonia aquifolium– Oregon-grape, Hydrastis canadensis – goldenseal, Coptis chinensis– Chinese goldthread, Tinospora cordifolia, Argemone mexicana– prickly poppy, and Eschscholzia californica), Phellodendron japonicum, and Berberis aquifolium. It is usually found in the roots, rhizomes, stems, and bark. These plants have been used as folk medicines for the treatment of gastrointestinal
disorders including diarrhea and gastroenteritis. Berberine is considered to be a predominantly selective Jak3 antagonist. Data from kinase assays and protein-compound docking simulation show that berberine blocked Jak3 catalytic activity after binding to the kinase domain of Jak3. Recent investigations prove that the alkaloid also activates Jak2/STAT3 pathway. In previous investigations we have shown the beneficial effect of berberine in adjuvant-induced arthritis. We have found that the alkaloid delayed the development of adjuvant arthritis when applied after its onset at a dose of 10 mg/kg. Also, we have established berberine’s anti-osteoclastogenic effect in vitro. The aim of the present study was to evaluate the effect of berberine on bone and cartilage erosion and on synovial cell and osteoblast senescence of erosive arthritis (3).

**Name**

Berberine

**Accession Number**

DB04115 (EXPT00672)

**Type**

Small Molecule

**Groups**

Approved, Investigational

**Description**

An alkaloid from Hydrastis canadensis L, Berberidaceae. It is also found in many other plants. It is relatively toxic parenterally, but has been used orally for various parasitic and fungal infections and as anti-diarrheal.

**Structure**

![Chemical Structure of Berberine]
1.4 IDENTIFICATION OF RESEARCH PROBLEM
In previous time the herbal drugs were not attracting scientists for development of novel drug delivery system due to processing, standardizing, extracting and identification difficulties. But now day with advancement in technologies novel drug delivery system new doors are opens for development of herbal drug delivery systems. Inflammatory diseases including different types of rheumatoid arthritis are very common throughout the world. Rheumatoid arthritis (RA) is a chronic progressive disease characterized by synovial inflammation, autoantibody production, and cartilage and bone destruction. The therapy of inflammation deals with the drug used to treat inflammatory and immune disorders. NSAID’s, glucocorticoids or so-called disease modifying drugs such as gold or methotrexate are prescribed for the treatment of RA. NSAID’s represents an indispensable place in the treatment of rheumatoid disorders. Administration of NSAID’s in the patients with congestive heart failure, renovascular and cirrhosis of the liver, activates renin angiotensin system may cause acute renal failure. Long term use of NSAID’s may cause infertility in women. The prolong term use of NSAID’s may lead to infertility and impotence in males. Since time immemorial, indigenous plants have been a major source of medicines. They are used in single or combination form for treating different types of inflammatory and arthritic conditions. Berberine with wide range of biological activity possesses low absorption. This was selected for the study as it poorly absorbed in the lower GIT and have short elimination half life. The floating microsphere beneficially alters the absorption of the drug and enhancing bioavailability. They prolong the dosing interval which will allow developing once a day formulation and thereby enhance patient compliance beyond the level of existing dosage forms by achieving the control over gastric residence time. Floating microspheres are gastro retentive drug delivery system based on non effervescent approach. They float over gastric content for long period of time. As the system floats over the gastric content the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

1.5 FLOATINGMICROSPHERE
The primary aim of oral controlled drug delivery is the most preferable route of drug delivery system is to achieve better bioavailability and release of drug from the system which should be predictable and reproducible, easy for administration, patient compliances and flexibility in formulation for effective therapy or to improve therapeutic efficiency of the drug through improved bioavailability. Gastro retentive dosage forms significantly extend for the period of
time, over which drug may be released and thus prolong dosing intervals and increase patient compliance. Gastric retention can be achieved by the mechanism of mucoadhesive or bioadhesion systems, expansion system, high density systems, magnetic systems, super porous hydrogels, raft forming systems, low density system and floating ion exchange resins. Floating drug delivery systems or hydro dynamically balance systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. The drug is released slowly at a desired rate from the system and drug residual systems are emptied from the stomach. This results in increase in the gastric residence time and a better control of qualification in plasma drug concentration. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1μm to 1000μm). Microspheres are sometimes referred to as micro particles. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material (Fig 1.2,1.3).

Hollow microspheres, micro balloons or floating micro particles are terms used synonymously for floating microspheres. Floating microspheres are, in a strict sense, spherical empty particles without a core (Fig 1.4). These are free-flowing particles, with size ranging from 1 to 1000μm. Kawashima have developed non-effervescent hollow polycarbonate microspheres by using an emulsion solvent evaporation method. This gastrointestinal transit-controlled preparation is designed to float on gastric juice with a specific density of less than one. This property results in delayed transit through the stomach. The drug is released slowly at desired rate, resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period.

**Types of Floating Drug Delivery System**

FDDS can be divided into two systems:

1. Effervescent systems
2. Non-effervescent systems
Fig 1.2: Formulation of Floating Microsphere.

Fig 1.3: Outer surface of a microsphere.

Fig 1.4: Inner Surface of a Microsphere.
1.5.1 Mechanism of Floatation of Microspheres
When microspheres come in contact with gastric fluid, the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However, a minimal gastric content is needed to allow proper achievement of buoyancy.

1.5.2 Mechanism of Drug Release from the Microspheres
The mechanism of drug release from multi Particulate can occur in the following ways:

**Diffusion:** On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

**Erosion:** Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

**Osmosis:** In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

1.5.3 Advantages of Floating Microspheres
a. Enhanced bioavailability.
b. Enhanced first-pass biotransformation.
c. Sustained drug delivery/reduced frequency of dosing.
d. Targeted therapy for local ailments in the upper GIT.
e. Reduced fluctuations of drug concentration.
f. Improved receptor activation selectivity etc.

**Disadvantages of Floating Microspheres**
A: These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
B: Not suitable for drugs that have solubility or stability problem in GIT etc.
1.6 PLAN OF WORK

Drug related studies
Drug identification test.
UV Spectroscopic studies.
FTIR Spectroscopic studies.

Formulation of Floating Microspheric system

Evaluation of Floating Microspheric system
Particle Size
Bulk Density
Tapped Density
Carr’s Index
Angle of Repose
Scanning Electron Microscopy
Sphericity of the Microsphere
Yield of Microsphere
Paw Thickness

Selection of Polymers

IN Vivo studies

1.7 EXCIPIENTS
Berberine hydrochloride
HPMC
PVP K30
Tween 80
Dichloromethane: ethanol (1:1)
Heavy liquid paraffin

1.8 CONCLUSION
BERBERINE HYDROCHLORIDE floating microsphere were manufactured by various methods but here I followed solvent evaporation using different levels and combination of the polymers HPMC, Tween 80 etc. The combination of both shows beneficial effects on rheumatic patients with increased bioavailability and buoyancy.
1.9 REFERENCES
1. Petya Ganova1, Lyudmila Belenska-Todorova2, T svetelina Doncheva3 and Nina Ivanovska1.
   a. Institute of Microbiology, Department of Immunology, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria.
   b. Medical Faculty, Sofia University, Bulgaria.
   c. Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy 13, Sofia, Bulgaria.
4. Abhishek Kumar 1, 2 and Brijesh Kr. Tiwari 2 Mewar University 1, Gangrar - 312901, Rajasthan, India. NKBR College of Pharmacy and Research Centre 2, MeeruArora, S., and Alij, A. A. (2005).
6. Abhishek Kumar 1, 2 and Brijesh Kr. Tiwari 2 Mewar University 1, Gangrar - 312901, Rajasthan, India. NKBR College of Pharmacy and Research Centre 2, Meerut - 250004, Uttar Pradesh, India.
7. Binu Chandran1 and Ajay Goel2 1Nirmala Medical Centre, Muvattupuzha, Kerala, India.
8. 2Baylor Research Institute and Sammons Cancer Center, Baylor University Medical Center, Dallas, TX, USA.